IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
AS DESIGNATED/ELECTED OFFICE

Application No:	10/XXX,XXX (continuation of 09/890,323)
Applicants:	Douglas P. CERRETTI
Filing Date	September 19, 2003
Title:	METALLOPROTEINASE-DISINTEGRIN POLYPEPTIDES
Docket No.:	2517-USB

Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REMARKS

Remarks begin on page 2 of this paper.

REMARKS

This application is filed with a new, clean copy of the specification that incorporates changes as described below.

In the Title:

The title has been changed to incorporate changes entered in the parent application (U.S. Serial No. 09/890,323).

In the Specification:

The specification has been changed to update the "CROSS REFERENCE TO RELATED APPLICATIONS" section, to correct typographical errors, and to remove text such as "http://" that could generate hyperlinks (see MPEP § 608.01). The changes to the specification paragraphs are shown by the marked-up text below and are referred to by the location of the changed paragraph in the presently provided specification.

The paragraph beginning at page 1, line 9, has been changed as follows:

This application is a continuation of U.S. application Serial No. 09/890,323, which is a 35 U.S.C. §371 filing of International Application Number PCT/US00/01338 having an international filing date of January 21, 2000 and published under PCT Article 21(2) in English on July 27, 2000, said International Application claiming the benefit of United States provisional application S.N. 60/116,670; S.N. 60/138,682; and S.N. 60/155,798; filed January 21, 1999; June 14, 1999; and September 27, 1999, respectively. The entire disclosures of these applications are relied upon and incorporated by reference herein.

The paragraph beginning at page 33, line 39, has been changed as follows:

For example, chromosomes can be mapped by radiation hybrid mapping. First, PCR is performed using the Whitehead Institute/MIT Center for Genome Research Genebridge4 panel of 93 radiation hybrids

(~~http://~~www-genome.wi.mit.edu/ftp/distribution/human_STS_releases/july97/rhmap/genebridge4.html). Primers are used which lie within a putative exon of the gene of interest and which amplify a product from human genomic DNA, but do not amplify hamster genomic DNA. The results of the PCRs are converted into a data vector that is submitted to the Whitehead/MIT Radiation Mapping site on the internet (~~http://~~www-seq.wi.mit.edu). The data is scored and the chromosomal assignment and placement relative to known Sequence Tag Site (STS) markers on the radiation hybrid map is provided. The following web site provides additional information about radiation hybrid mapping: ~~http://~~www-genome.wi.mit.edu/ftp/distribution/human_STS_releases/july97/07-97.INTRO.html~~)~~.

The paragraph beginning at page 42, line 16, has been changed as follows:

As to the specific use of the polypeptides and fragmented peptides of the invention as molecular weight markers, the fragmentation of the polypeptide of SEQ ID NOs:4-6 and 12-16 with cyanogen bromide in the absence of glycosylation generates a unique set of fragmented peptide molecular weight markers with molecular weights as set forth in Table 1 ~~on the following page~~.

The paragraph beginning at page 47, line 21, has been changed as follows:

As noted above, SVPH-1a, SVPH-1b, and SVPH-1c diverge from the consensus zinc-binding cluster (**HEXXHXXGXXHD**) (SEQ ID NO:31) in the catalytic domain with a Glu to His change at position 333. To analyze these proteins further, DNA and protein sequence multiple alignments of all known mammalian ADAMs (~~http://~~www.med.virginia.edu/~jag6n/adams.html) were produced using the PILEUP program from the Wisconsin Package (Wisconsin Package 10.1, Genetics Computer Group, Madison, WI). Protein multiple alignments were generated using the modified PAM scoring matrix of Gribskov and Burgess (Gribskov, M. et al., *Nucleic Acids Res.*, 14:6745-6763 (1986)) provided in the Wisconsin Package, with gap-open and gap-extend penalties of 30 and 1, respectively. Nucleic acid multiple alignments were generated using a scoring matrix with A, C, G, T matches scoring unity, mismatches scoring zero, and gap-open and gap-extend penalties of 5 and 1 respectively. Unrooted maximum parsimony trees were estimated by the Wisconsin Package implementation of PAUP (version 4.0), starting from multiple alignments produced by PILEUP. PAUP parameters were set to use accelerated transformation character-state optimization with unordered, equally weighted characters.

In the Claims:

The claims have been replaced with claims 1-31 as follows:

1. An isolated polypeptide having disintegrin activity and comprising amino acids 389 through 491 of SEQ ID NO:12.

2. The isolated polypeptide of claim 1 wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:12, SEQ ID NO:13, and SEQ ID NO:14.

3. The isolated polypeptide of claim 1 further comprising an amino acid sequence selected from the group consisting of amino acids 1 through 15 of SEQ ID NO:12, amino acids 16 through 188 of SEQ ID NO:12, amino acids 189 through 388 of SEQ ID NO:12, amino acids 492 through 675 of SEQ ID NO:12, amino acids 676 through 698 of SEQ ID NO:12, amino acids 699 through 766 of SEQ ID NO:12, amino acids 699 through 787 of SEQ ID NO:13, and amino acids 699 through 820 of SEQ ID NO:14.

4. The isolated polypeptide of claim 1 further comprising the amino acid sequence of a polypeptide selected from the group consisting of a poly-His peptide, a FLAG peptide, a peptide linker, a leucine zipper domain, and an Fc polypeptide.

5. The isolated polypeptide of claim 1 in non-glycosylated form.

6. An isolated polypeptide having disintegrin activity encoded by a nucleic acid molecule selected from the group consisting of:

(a) an isolated nucleic acid molecule comprising a DNA sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9;

(b) an isolated nucleic acid molecule encoding an amino acid sequence comprising the sequence selected from the group consisting of amino acids 389 through 491 of SEQ ID NO:12, SEQ ID NO:12, SEQ ID NO:13, and SEQ ID NO:14;

(c) an isolated nucleic acid molecule that encodes a polypeptide having disintegrin activity and that hybridizes to either strand of a denatured, double-stranded DNA comprising a nucleic acid sequence of (a) under hybridization conditions of 50% formamide and 6XSSC, at 42°C with washing conditions of 68°C, 0.2X SSC, 0.1% SDS; and

(d) an isolated nucleic acid molecule degenerate from SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9 as a result of the genetic code.

7. The isolated polypeptide of claim 6 having a molecular weight selected from the group consisting of approximately 86,983; 89,459; and 92,781 Daltons as determined by SDS-PAGE.

8. The isolated polypeptide of claim 6 in non-glycosylated form.

9. The isolated polypeptide of claim 6, wherein the polypeptide comprises amino acids 389 through 491 of SEQ ID NO:12.

10. The isolated polypeptide of claim 9 further comprising an amino acid sequence selected from the group consisting of amino acids 1 through 15 of SEQ ID NO:12, amino acids 16 through 188 of SEQ ID NO:12, amino acids 189 through 388 of SEQ ID NO:12, amino acids 492 through 675 of SEQ ID NO:12, amino acids 676 through 698 of SEQ ID NO:12, amino acids 699 through 766 of SEQ ID NO:12, amino acids 699 through 787 of SEQ ID NO:13, and amino acids 699 through 820 of SEQ ID NO:14.

11. The isolated polypeptide of claim 6, wherein the polypeptide comprises SEQ ID NO:12.

12. The isolated polypeptide of claim 6, wherein the polypeptide comprises SEQ ID NO:13.

13. The isolated polypeptide of claim 6, wherein the polypeptide comprises SEQ ID NO:14.

14. The isolated polypeptide of claim 6 further comprising the amino acid sequence of a polypeptide selected from the group consisting of a poly-His peptide, a FLAG peptide, a peptide linker, a leucine zipper domain, and an Fc polypeptide.

15. A polypeptide having disintegrin activity and encoded by a recombinant nucleic acid, wherein the polypeptide is expressed by a method comprising culturing a host cell comprising said recombinant nucleic acid under conditions promoting expression of the polypeptide, and wherein said recombinant nucleic acid comprises a nucleotide sequence encoding the polypeptide and selected from the group consisting of:

(a) SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9;

(b) a nucleotide sequence encoding an amino acid sequence comprising a sequence selected from the group consisting of amino acids 389 through 491 of SEQ ID NO:12, SEQ ID NO:12, SEQ ID NO:13, and SEQ ID NO:14;

(c) a nucleotide sequence that encodes a polypeptide having disintegrin activity and that hybridizes to either strand of a denatured, double-stranded DNA comprising a nucleotide sequence of (a) under hybridization conditions of 50% formamide and 6XSSC, at 42°C with washing conditions of 68°C, 0.2X SSC, 0.1% SDS; and

(d) a nucleotide sequence degenerate from SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9 as a result of the genetic code.

16. The polypeptide of claim 15, wherein the polypeptide is expressed by a method further comprising purifying the expressed polypeptide.

17. The polypeptide of claim 15, wherein the polypeptide is expressed by a method comprising culturing a host cell selected from the group consisting of bacterial cells, yeast cells, plant cells, and animal cells.

18. The polypeptide of claim 15, wherein the polypeptide is expressed by a method comprising culturing a mammalian host cell.

19. The polypeptide of claim 15 having a molecular weight selected from the group consisting of approximately 86,983; 89,459; and 92,781 Daltons as determined by SDS-PAGE.

20. The polypeptide of claim 15 in non-glycosylated form.

21. The polypeptide of claim 15, wherein the polypeptide comprises amino acids 389 through 491 of SEQ ID NO:12.

22. The polypeptide of claim 21 further comprising an amino acid sequence selected from the group consisting of amino acids 1 through 15 of SEQ ID NO:12, amino acids 16 through 188 of SEQ ID NO:12, amino acids 189 through 388 of SEQ ID NO:12, amino acids 492 through 675 of SEQ ID NO:12, amino acids 676 through 698 of SEQ ID NO:12, amino acids 699 through 766 of SEQ ID NO:12, amino acids 699 through 787 of SEQ ID NO:13, and amino acids 699 through 820 of SEQ ID NO:14.

23. The polypeptide of claim 15, wherein the polypeptide comprises SEQ ID NO:12.

24. The polypeptide of claim 15, wherein the polypeptide comprises SEQ ID NO:13.

25. The polypeptide of claim 15, wherein the polypeptide comprises SEQ ID NO:14.

26. The polypeptide of claim 15 further comprising the amino acid sequence of a polypeptide selected from the group consisting of a poly-His peptide, a FLAG peptide, a peptide linker, a leucine zipper domain, and an Fc polypeptide.

27. An isolated polypeptide having disintegrin activity and having at least 90% amino acid identity with amino acids 389 through 491 of SEQ ID NO:12.

28. The isolated polypeptide of claim 27, wherein the polypeptide has at least 95% amino acid identity with amino acids 389 through 491 of SEQ ID NO:12.

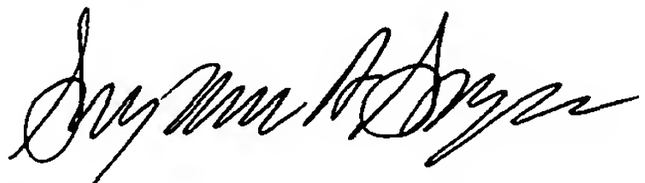
29. The isolated polypeptide of claim 27, wherein the polypeptide has at least 98% amino acid identity with amino acids 389 through 491 of SEQ ID NO:12.

30. The isolated polypeptide of claim 27, wherein the polypeptide further comprises an amino acid sequence selected from the group consisting of amino acids 1 through 15 of SEQ ID NO:12, amino acids 16 through 188 of SEQ ID NO:12, amino acids 189 through 388 of SEQ ID NO:12, amino acids 492 through 675 of SEQ ID NO:12, amino acids 676 through 698 of SEQ ID NO:12, amino acids 699 through 766 of SEQ ID NO:12, amino acids 699 through 787 of SEQ ID NO:13, and amino acids 699 through 820 of SEQ ID NO:14.

31. The isolated polypeptide of claim 27, wherein the polypeptide further comprises the amino acid sequence of a polypeptide selected from the group consisting of a poly-His peptide, a FLAG peptide, a peptide linker, a leucine zipper domain, and an Fc polypeptide.

If a telephone interview would be helpful in advancing the prosecution of this application, Applicants' attorney invites the Examiner to contact her at the number provided below.

Respectfully submitted,



Amgen Inc.
Law Department
51 University Street
Seattle, WA 98101

Suzanne A. Sprunger, Ph.D.
Attorney for Applicants
Registration No. 41,323
Telephone (206) 265-4071